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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/865,553	05/29/2001	Karola Rittner	03275P050	4015

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	**PAPER NUMBER**
1637	23

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/865,553	RITTNER ET AL.	
	Examiner	Art Unit	
	Teresa E Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *4,15 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 May 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I (claims 1-14, SEQ ID NO: 2) in Paper No. 21 is acknowledged.

2. Claims 4, 15 and 16 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 21.

3. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims under consideration

4. Claims 1-16 are pending, with claims 4, 15 and 16 withdrawn from consideration. Claims 1-3, 5-14 will be examined, with claim 5 considered as reading on SEQ ID NO: 2.

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. European Patent Applications No. 00 44 0162.6, filed May 26, 200, and 01 44 0049.3, filed February 27, 2001, have been received.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on November 29, 2001 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

3. The drawings were received on June 3, 2003. These drawings are accepted.

4. The drawings are objected to because:

A) Figure 9 has parts 9A1 and 9A2, which are two different figures, and there is no description of these in the specification,

B) Figure 10 has parts 10D1 and 10D2, which are two different figures, and there is no description of these in the specification. Either the figures should be renumbered, or appropriate descriptions should be provided.

C) Figure 11 has parts 11, 11B, etc., whereas the description refers to Fig. 1A, 1B, etc. Figure 11 should be relabeled as 11A.

A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

5. The abstract of the disclosure is objected to because of legal phrase "said peptide" in line 3. Correction is required. See MPEP § 608.01(b).

6. The disclosure is objected to because of the following informalities:

A) There two Examples No. 11 in the specification, one on page 54, the other on page 55.

B) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. The hyperlinks are present on page 1, lines 25 and 26, and on page 35, lines 3-9.

Appropriate correction is required.

Claim interpretation

7. "Cationic peptide" is interpreted as a peptide with a net positive charge. "Anionic substance" is interpreted as any compound with a negative charge.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1-3, 6-8 and 10-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohmori et al. (Biochem. Biophys. Res. Comm., vol. 245, pp. 259-265, 1998).

Regarding claim 1, Ohmori et al. teach five cationic peptides consisting of leucines (L) and lysines (K) residues, with compositions of 13L+ 5K (13-5), 11L+7K (11-7), 9L+9K (9-9), 7L+11K (7-11) and 5L+13K (5-13). These peptides had positive charges of +5, +7, +9, +11 and +13, respectively, and did not contain acidic residues (Fig. 1). These peptides were capable of causing membrane disruption, as evidenced by the fact that they mediated transfection of plasmid DNA encoding luciferase into COS-7 cells (page 262, third paragraph; Fig. 5).

Regarding claim 2, Ohmori et al. teach five cationic peptides consisting of leucines (L) and lysines (K) residues, which do not contain glutamic acid (Fig. 1).

Regarding claim 3, Ohmori et al. do not specifically teach molecular weights (MW) of the peptides, but knowing that MW of leucine is 131.2 and of lysine is 146.2, the peptides had the following MW: 2436.6 D (13-5), 2466.6 D(11-7), 2496.6 D (9-9), 2526.6 D (7-11) and 2556.6 D (5-13), therefore all of them had MW less than 5 kD (= 5000 D).

Regarding claim 6, Ohmori et al. teach a complex for transferring an anionic substance into a cell, the complex comprising one of the peptides and an anionic substance (= DNA) (page 262, third paragraph; Fig. 5).

Regarding claim 7, Ohmori et al. teach the complex further comprising another peptide which is capable of causing membrane disruption, LAEL-LAEl-LAEL (page 263, the last paragraph; page 264, first paragraph; Fig. 6).

Regarding claim 8, Ohmori et al. teach the anionic substance being DNA (= nucleic acid) (page 262, third paragraph; Fig. 5).

Regarding claims 10 and 11, Ohmori et al. teach the sizes of complexes being less than 500 nm and between 20 and 100 nm (Fig. 4 C-E).

Regarding claim 12, Ohmori et al. teach the ratio of positive charges to negative charges in the complex of peptide and DNA was varied from 0.1 to 4 (page 261, first paragraph) or from 0.1 to 16 (page 263, last paragraph; Fig. 6), which is within the claimed range of between 0.05 and 20.

Regarding claim 13, Ohmori et al. teach the ratio of positive charges to negative charges in the complex of peptide and DNA was 1. 0 (page 261, first paragraph and Fig. 6).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 9 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohmori et al. (Biochem. Biophys. Res. Comm., vol. 245, pp. 259-265, 1998) in view of Smith et al. (WO 96/40958; cited in the IDS).

A) Ohmori et al. teach transporting of plasmid DNA in a complex with cationic peptide into COS-7 cells and such complex being efficient for gene transfer (page 265, the last two sentences), but they do not teach the nucleic acid comprising a therapeutically useful gene or a composition comprising the nucleic acid-peptide complex and a carrier.

B) Regarding claim 9, Smith et al. teach a nucleic acid transporter system for delivery of nucleic acids into cells (Abstract). The transporter system comprises a peptide which is capable of membrane disruption (page 39, lines 20-36; page 40-42; page 43, lines 1-7) complexed with nucleic acid comprising a therapeutically useful gene and elements enabling its expression, namely, a nucleic acid encoding LDL-receptor under the control of CMV enhancer and promoter elements.

Regarding claim 14, Smith et al. teach a composition comprising the nucleic acid-peptide complex (= nucleic acid transporter) and an amorphous powder, PVP, for administration by inhalation (page 67, lines 4-14 and 28-36).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have used the LDL-receptor gene of Smith et al. complexed with the cationic peptide of Ohmori et al. to deliver the LDL-receptor gene to cells. The motivation to do so, provided by Smith et al., would have been that LDL-receptor deficiency leads to coronary atherosclerosis and myocardial infarction (page 63, lines 5-36).

12. Claims 1, 5, 6, 8, 9 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al. (WO 96/40958; cited in the IDS) in view of Wyman et al. (Biochemistry, vol. 36, pp. 3008-3017, 1997; cited in the IDS).

A) Regarding claim 1, Smith et al. teach peptides (page 9, lines 34-37; page 10, lines 1-18; page 34, lines 10-35; page 35, lines 1-15) which are capable of membrane disruption (page 39, lines 20-36; page 40-42; page 43, lines 1-7).

Regarding claim 5, Smith et al. teach a peptide JTS-1 with amino acid sequence of GLFEALLELLESLWELLLEA (page 10, line 18; page 34, line 11).

Regarding claim 6, Smith et al. teach a complex for transferring an anionic substance into a cell, the complex comprising JTS-1 and an anionic substance (= DNA plasmid) (page 43, lines 29-36; page 44, lines 1-15).

Regarding claim 8, Smith et al. teach the anionic substance being nucleic acid (= DNA plasmid) (page 43, lines 29-36; page 44, lines 1-15).

Regarding claim 9, Smith et al. teach the complex in which a nucleic acid comprises a therapeutically useful gene sequence and elements enabling its expression, namely, a nucleic acid encoding LDL-receptor under the control of CMV enhancer and promoter elements. LDL-receptor deficiency leads to coronary atherosclerosis and myocardial infarction (page 63, lines 5-36).

Regarding claim 14, Smith et al. teach a composition comprising the nucleic acid-peptide complex (= nucleic acid transporter) and an amorphous powder, PVP, for administration by inhalation (page 67, lines 4-14 and 28-36).

B) Smith et al. do not teach cationic peptides. Smith et al. teach that the glutamic acids of JTS-1 could be replaced with basic amino acids (page 10, lines 28-30) and that lytic activity of the peptide can be controlled by introduction of lysine, arginine and histidine into the hydrophilic phase of JTS-1 (page 11, lines 9-11). The only difference between JTS-1 and SEQ ID NO: 2 is replacement of glutamates (E) with lysines (K) (see sequence alignment).

C) Wyman et al. teach conversion of an anionic peptide GALA, which contains six glutamate residues on the hydrophilic face of its helical structure with KALA, which contains seven lysine residues on the hydrophilic face of its helical structure (Fig. 1), so that the modified peptide had a net positive charge (page 3012, second paragraph). The peptide caused membrane

destabilization in liposomes in the absence of DNA (page 3012, fourth paragraph) and in the presence of DNA oligonucleotides (page 3012, last paragraph; page 3013, first paragraph; Fig. 3). Complexes of fluorescently-labeled oligonucleotides complexed with KALA were efficiently taken up by cell nuclei, in contrast to similar complexes made with GALA (Fig. 7). In addition, plasmid DNA was efficiently transfected into cells when complexed with KALA (Fig. 8).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have made the substitution of glutamates for lysines according to Wyman et al. in the peptide of Smith et al. The motivation to do so, provided by Wyman et al., would have been that such a peptide not only destabilized membranes, but also bound DNA and mediated gene transfer into cells (page 3015, fifth paragraph). In addition, positively charged peptide effectively disrupted both neutral and negatively charged membranes (page 3016, fifth paragraph). Finally, as stated by Wyman et al. "We have designed and synthesized a novel peptide capable of condensing DNA and causing membrane leakage, nuclear delivery of oligonucleotides, and transfection of plasmid DNA in various cell lines. This peptide has a number of advantages over previously reported gene delivery systems. First, it is convenient to synthesize; second, it is efficient at mediating transfection in cells without the need for other agents such as chloroquine or adenoviral endosomal disruption agents. It provides a starting point for additional improvements in the sequence that might provide ligands for cell surface or cytoplasmic receptors to improve DNA trafficking into and through the target cell. Finally, it can serve as a platform to help unravel the roles of DNA binding/dissociation and membrane destabilization in the transfection process." (page 3016, last paragraph).

13. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E Strzelecka whose telephone number is (703) 306-5877. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

JEFFREY FREDMAN
PRIMARY EXAMINER

TS
September 12, 2003